ORIGINAL ARTICLE

CONTENTS

Hepatoprotective role of vildagliptin in CLP-induced sepsis in mice

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ABSTRACT

Aim: The current study aimed to determine the underlying mechanisms of protective effect of vildagliptin against sepsis induced liver injury.

Materials and methods: Male mice were randomly allocated to sham group, Cecal Ligation and Puncture group, Dimethyl sulfoxide group and vildagliptin group (20 mg/kg). Cecal Ligation and Puncture operation was established for mice. After 24 hours of Cecal Ligation and Puncture, serum levels of Alanine Transaminase, Aspartate Transaminase and histopathological changes of liver tissue were evaluated. Our study assessed IL-6, Macrophage migration inhibitory factor, Intercellular Adhesion Molecule 1, caspase-11, Malondialdehyde, Superoxide dismutase and Microtubule-associated protein 1A/1B-light chain 3 by ELISA method as well as Wnt and B-catenin by RT-qPCR.

Results: The results of current study showed that vildagliptin administration significantly declined serum levels of Alanine Transaminase and Aspartate Transaminase in addition to reduced histopathological changes of liver. Vildagliptin markedly inhibited elevation of IL-6, MIF, Intercellular Adhesion Molecule 1, MDA, caspase-11 and Wnt/B-catenin. Vildagliptin elevated Superoxide dismutase and Microtubule-associated protein 1A/1B-light chain 3 in hepatic tissue.

Conclusions: Vildagliptin has Hepatoprotective effect during endotoxemia induced liver injury through modulation inflammatory and oxidative stress markers in addition to down regulation of Wnt/B-catenin pathway.

KEY WORDS: vildagliptin, Cecal Ligation and Puncture, sepsis, Wnt/B-catenin pathway, oxidative stress, autophagy, apoptosis

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ABBREVIATIONS

CLP - Cecal Ligation and Puncture
DMSO - Dimethyl Sulfoxide
ALT - Alanine Transaminase
AST - Aspartate Transaminase
MIF - Macrophage Migration Inhibitory Factor
ICAM-1 - Intercellular Adhesion Molecule 1
MDA - Malondialdehyde
SOD - Superoxide Dismutase
LC3 - Microtubule-associated protein 1A/1B-light chain 3
GLP-1 - Glucagon-Like Peptide-1

INTRODUCTION

Sepsis can be defined as a serious inflammatory response syndrome caused by infection with high morbidity and mortality [1]. They have been reported the number of deaths caused by multiorgan failure is about 11 million, which represent a great threat to human worldwide [2]. The liver is considered as substantial organ and is involved in various physiological process including detoxification, metabolism and immunity. Sepsis induced liver injury resulting in abnormalities of biochemical investigations and hepatic insufficiency or even liver failure [3]. Early identification and intervention of liver injury result in improvement survival rates [4]. Sepsis can be initiated by a number of pathogens such as parasites, bacteria, viruses and fungi. The main characteristics of sepsis including intense inflammatory response, activation of coagulation and immune suppression [5-6]. The pathogenesis of sepsis includes various mechanisms such as microcirculation disorder, immune response, inflammatory mediators' release and pathogen invasion [7]. The Wnt /B- catenin pathway has concerned as topic of interest among several molecular mechanisms contributed to pathogenesis of sepsis. Wnt/B-catenin elevation has been detected in sepsis and inhibition attenuated inflammatory response and mitigated sepsis induced organ injury. Additionally, aberrant activation of Wnt/ B-catenin signaling pathway

has been implicated in different diseases including degenerative disease and cancer [8]. Vildagliptin is a hypoglycemic agent related to class DPP-4 inhibitor, used for treatment type 2 diabetics through inhibit degradation of glucagon-like peptide-1 (GLP-1) [9]. Previous studies documented that vildagliptin ameliorated hepatic damaged induced by ischemia/reperfusion *via* suppression inflammatory, oxidative stress and apoptotic markers [10]. The present study aimed to investigate the potential Hepatoprotective effect of vildagliptin against sepsis induced liver injury.

MATERIALS AND METHODS

A total of twenty-four Swiss albino male mice, weighting 25-35 gm and aged 8-12 weeks, were randomly distributed into following groups 1- sham group: mice subjected to anesthesia and laparotomy procedure, 2- CLP group: mice subjected to CLP procedure, 3- DMSO group: mice administered an equivalent volume of DMSO intraperitoneal 1h before CLP procedure 4- Vildagliptin group: mice received 20 mg/Kg intraperitoneal 1 hour prior CLP procedure. CLP procedure was established as described previously [11-12]. Anesthetized all experimental mice by intraperitoneal solution of ketamine (100 mg/kg) and xylazine (10 mg/kg). The abdomen was shaved, disinfected and one cm midline laparotomy to exposed cecum. Then cecum was tightly ligated at the base below ileocecal valve, perforated twice with 20-gauge needle size and squeezed in order to extrude feces from perforation regions. Consequently, the cecum was returned to peritoneal cavity and the skin was closed with 6.0 silk. The experimental mice were resuscitated by subcutaneous injection 1 ml 0.9% saline solution and supplied free access of food and water. Blood samples were collected to investigate liver enzymes (aspartate transaminase, AST and alanine transaminase, ALT) and macrophage migration inhibitory factor (MIF). A small part of liver was excised for histopathological examination and the rest of liver tissue was homogenized to measure intercellular adhesion molecule 1 (ICAM-1), interleukin-6 (IL-6), caspase-11, malondialdehyde (MDA), superoxide dismutase (SOD) and microtubule-associated protein 1A/1B-light chain 3 (LC3) in addition to the gene levels of Wnt (F CAAATAGGCAGCCGAGAGAC, R TGCAACCACAGGTAGACAGC) and B-catenin (F GTCAGCTCGTGTCCTGTGAA, R GATCTGCATGCCCTCATCTA) using qPCR. All laboratory and histopathological tests were performed after CLP procedure.

REAGENTS

Vildagliptin was purchased from AK Scientific, USA. ELISA kit of SOD and MDA were obtained from Bioassay Technology Laboratory BT LAB. Additionally, ELISA kit of caspase-11, ICAM-1, MIF, LC3 and IL-6 were purchased from SunLong Biotech CO. Ketamine vial (100 mg/ml) was received from Alfasan and xylazine (20 mg/ml) was from Micropets.

HISTOPATHOLOGICAL EXAMINATION

Liver tissues were kept in buffered formaldehyde solution 10%, then processed and embedded in paraffin. The section was cut to 5 µm thick and stained with hematoxylin and eosin (H&E). Liver histopathological score from 0 to 3. Score 0 when no pathological changes observed, score 1: is considered mild, score 2: moderate, score 3 is sever [11].

STATISTICAL ANALYSIS

Prisms 9.5 software used for analysis. All measurement data were expressed as mean ± standard error of mean. One-way ANOVA followed by Bonferroni test for comparison between groups. Kruskal-Wallis test was used for comparison histology scores. $P<0.05$ was considered statistically significant.

ETHICS APPROVAL

All experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at Kufa University after submitting the required applications (letter number 20549-29/8/2024).

RESULTS

EFFECT OF VILDAGLIPTIN ON SERUM LEVELS OF ALT AND AST

Significantly elevated serum concentration of both ALT and AST were detected in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly decreased the level of ALT and AST in septic mice. DMSO showed no significant effect on ALT and AST levels when given to septic mice (Fig. 1A-B).

Mice of sham group exposed to laparotomy procedure only. The mice of CLP group were exposed to CLP operation for 24 h. Mice received either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham groups) 1 h prior CLP operation. Serum liver enzymes were measured using spectrophotometry. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

EFFECT OF VILDAGLIPTIN ON HEPATIC IL-6, HEPATIC ICAM-1 AND SERUM MIF LEVEL

Significantly elevated tissue concentration of IL-6, ICAM-1 and serum MIF were detected in the CLP group

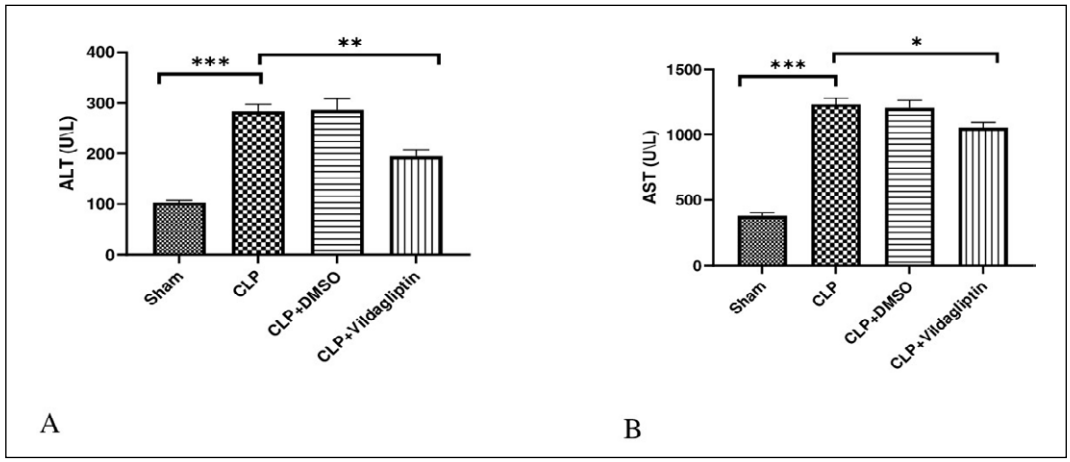

Fig 1. Effect of vildagliptin on serum levels of ALT (A) and AST (B)
Data are presented as mean ±SEM, n=6/group; *p<0.05, **p<0.01, ***p<0.001.
Source: Own materials

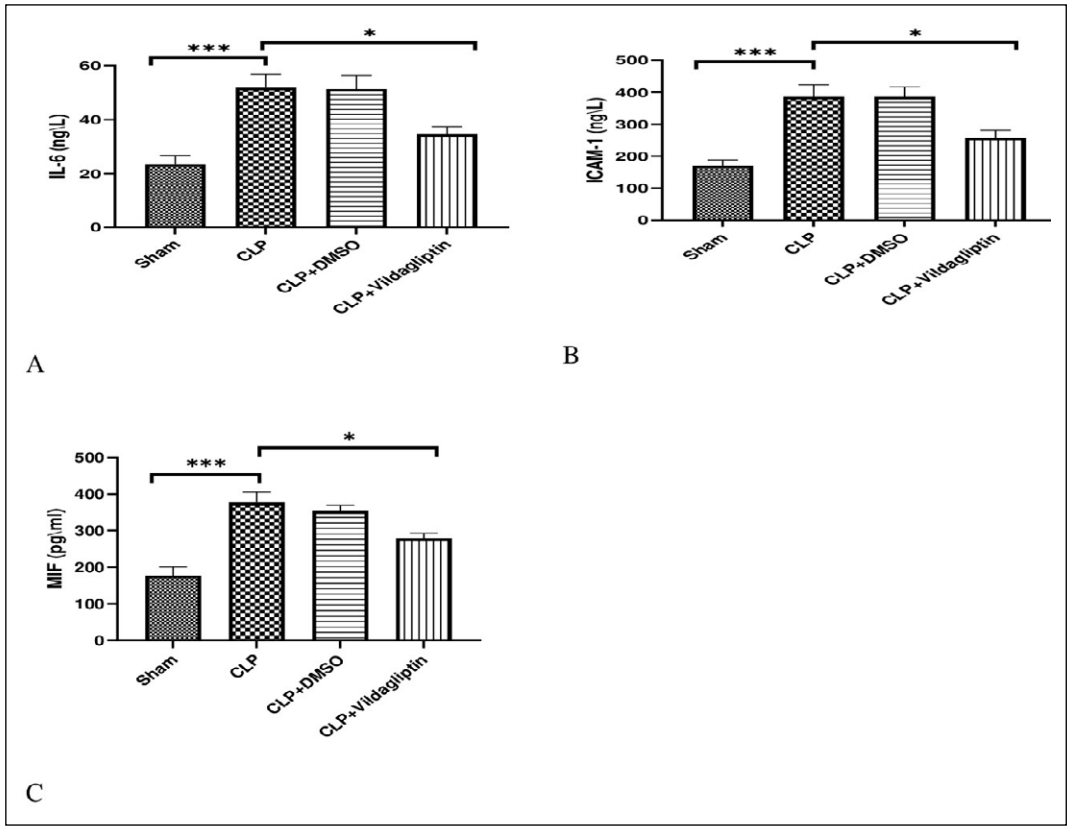

Fig. 2. Effect of vildagliptin on hepatic levels of IL-6 (A), hepatic ICAM-1 (B) and serum MIF (C)
Data are presented as mean ±SEM, n=6/group; *p<0.05, ***p<0.001.
Source: Own materials

in comparison with sham group. Pretreatment with vildagliptin significantly decreased levels of IL-6, ICAM-1 and MIF. DMSO did not affect IL-6, ICAM-1 and serum MIF levels when given to septic mice (Fig. 2A-C).

Mice of CLP group were exposed to CLP operation for 24 h, mice of sham group exposed to laparotomy procedure only. Mice received either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham group) 1h before CLP operation. Liver IL-6, liver ICAM-1 and serum MIF were measured using ELISA kit. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

EFFECT OF VILDAGLIPTIN ON HEPATIC LC3 LEVEL

Level of LC3 in the liver was significantly declined in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly elevated level of LC3. DMSO showed no significant impact on LC3 levels when given to CLP mice (Fig. 3).

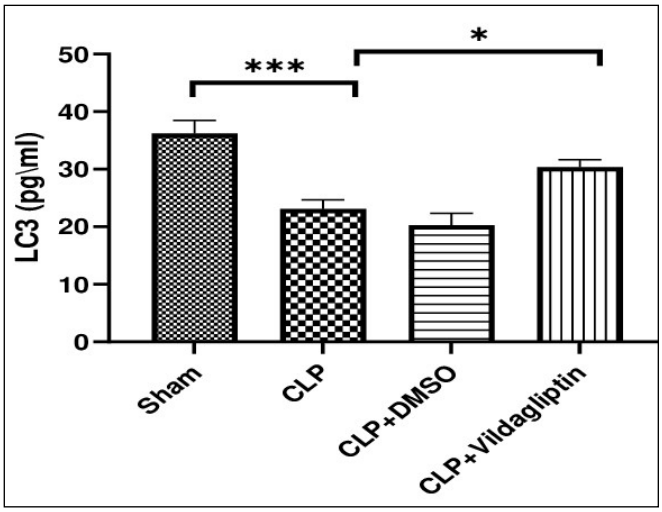

Fig. 3. Effect of vildagliptin on hepatic LC3 level
Data are presented as mean ±SEM, n=6/group; *p<0.05, ***p<0.001
Source: Own materials

Mice of CLP group were exposed to CLP operation for 24 h, while mice of sham group exposed to laparotomy procedure only. Mice were administered either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham groups) 1h before CLP operation. Liver LC3 was measured using ELISA kit. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

EFFECT OF VILDAGLIPTIN ON HEPATIC MDA AND HEPATIC SOD LEVELS

Significantly lowered tissue concentration of MDA was detected in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly lowered level of MDA (Fig. 4A). Hepatic level of SOD was significantly declined in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly elevated level of SOD (Fig. 4B). Pretreatment of septic mice with DMSO showed no significant impact on MDA and SOD levels.

Mice of sham group exposed to laparotomy procedure only. The mice of CLP group were exposed to CLP operation for 24 h. Mice were administered either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham group) 1h before CLP operation. Liver MDA and SOD were measured using ELISA kit. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

EFFECT OF VILDAGLIPTIN ON HEPATIC CASPASE-11 LEVEL

Significantly elevated tissue concentration of caspase-11was detected in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly decreased hepatic level of caspase-11. DMSO showed no significant change on caspase-11 levels when given to septic mice (Fig. 5).

Mice of sham group exposed to laparotomy procedure only. Mice of CLP group were exposed to CLP operation for 24 h. Mice received either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham groups) 1h before CLP operation. Liver caspase-11 was measured using ELISA kit. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

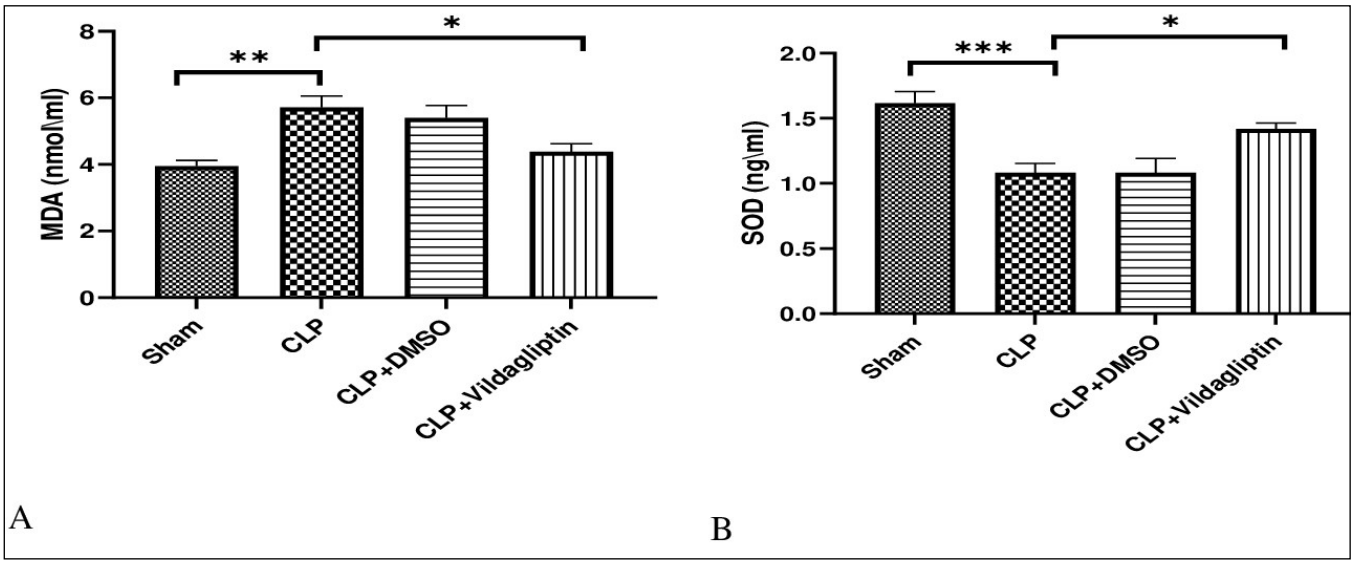

Fig. 4. Effect of vildagliptin on hepatic MDA and SOD levels
Data are presented as mean ±SEM, n=6/group; *p<0.05, **p<0.01, ***p<0.001
Source: Own materials

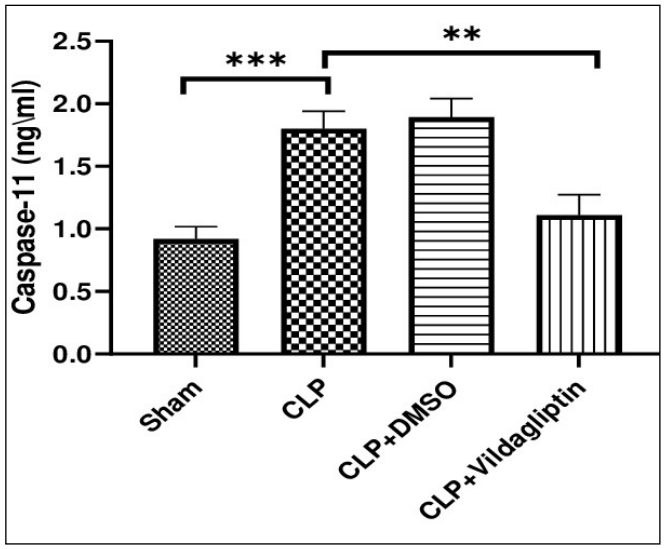

Fig. 5. Effect of vildagliptin on hepatic caspase-11 level
Data are presented as mean ±SEM, n=6/group; **p<0.01, ***p<0.001.
Source: Own materials

EFFECT OF VILDAGLIPTIN ON HEPATIC WNT/B-CATENIN PATHWAY

Significantly lowered tissue ΔCT levels of Wnt and B-catenin were detected in the CLP group in comparison with sham group. Pretreatment with vildagliptin significantly elevated ΔCT levels of Wnt and B-catenin. DMSO showed no significant impact on both tissue ΔCT levels of Wnt and B-catenin when given to septic mice (Fig. 6A-B).

Mice of sham group exposed to laparotomy procedure only. Mice of CLP group were exposed to CLP operation for 24 h. Mice received either vildagliptin (20 mg/kg), DMSO or left untreated (CLP and sham groups) 1h before CLP operation. Liver Wnt and B-catenin were measured using RT-PCR. Statistical analysis was performed using one-way ANOVA followed by Bonferroni test.

VILDAGLIPTIN TREATMENT ALLEVIATES HISTOLOGICAL CHANGES OF THE LIVER IN SEPTIC MICE

In sham group, there is no histological changes as showed in figure 7A. The CLP group exhibited sever histopathological changes characterized by inflammatory cell infiltration, cytoplasmic eosinophilia and necrosis. The histopathological change of CLP was significantly elevated as compared with sham group. Vildagliptin treatment was significantly reduced sepsis induced pathological changes (Fig. 7B-E).

Liver histopathological score in study group. The mice of CLP group were exposed to CLP operation for 24 h, mice of sham group exposed to laparotomy procedure only (sham group score 0). Mice received either (20 mg/kg), DMSO or left untreated (CLP and sham group) 1h before CLP operation. Histology changes were assessed by Kruskal-Wallis test (Fig. 8).

DISCUSSION

Sepsis, a life threating condition characterized by severe organ dysfunction resulted from uncontrolled host response to infection [13]. The pathophysiology mechanisms of sepsis induced organ dysfunction are related to intense inflammatory response, tissue hypoperfusion and intravascular coagulation [14]. The

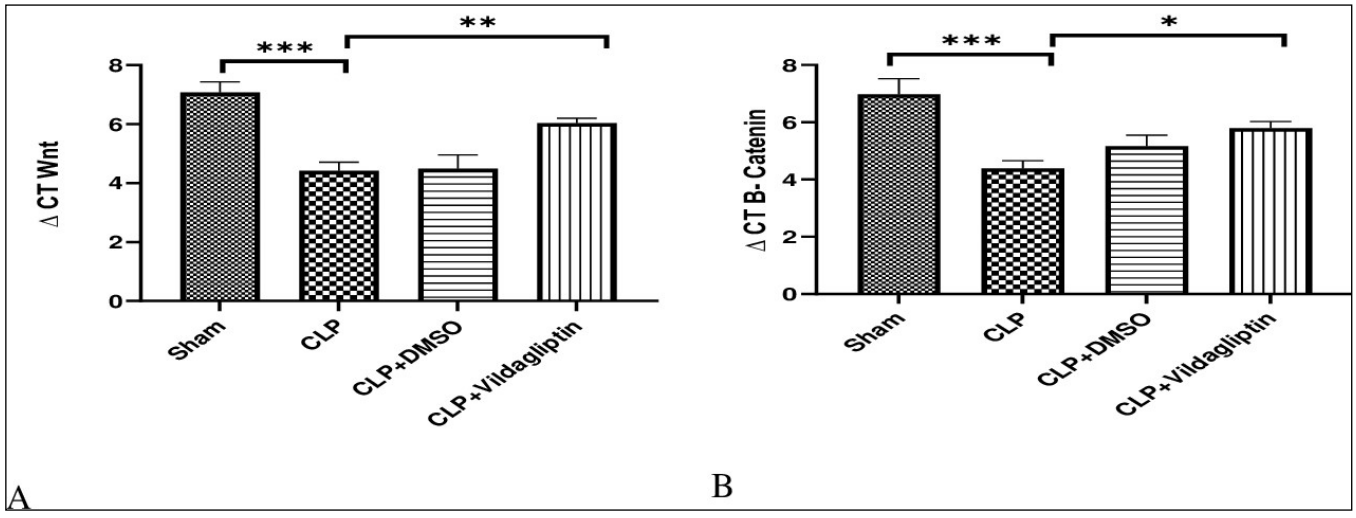

Fig. 6. Effect of vildagliptin on hepatic Wnt **(A)** /B-catenin pathway **(B)**
Data are presented as mean ±SEM, n=6/group *p<0.05, **p<0.01, ***p<0.001
Source: Own materials

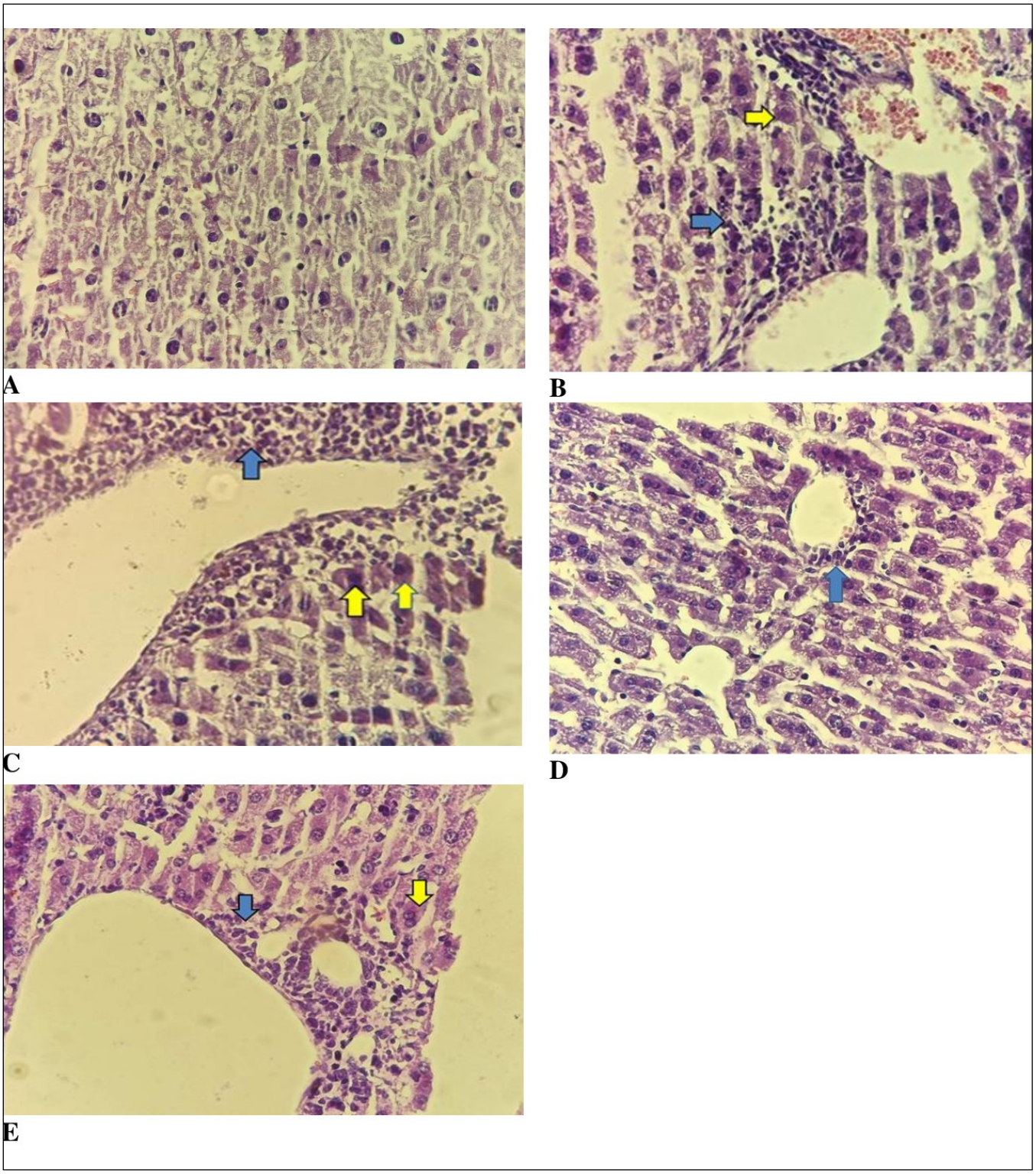

Fig. 7. A - Photomicrograph of hepatic section for sham group showed no evidence of inflammation or necrosis; score 0, H&E, x400; **B** - Photomicrograph of hepatic section for DMSO group showed sever periportal chronic inflammatory cell infiltration (blue arrow), with regions of pyknosis, cytoplasmic eosinophilia and necrosis (yellow arrows); score 3, H&E, x400; **C** - Photomicrograph of hepatic section for CLP group showed sever periportal and centrilobular chronic inflammatory cell infiltration (blue arrow), with focal regions cytoplasmic eosinophilia (apoptotic bodies) pyknosis and necrosis in the interface area (yellow arrows); score 3, H&E, x400; **D** - Photomicrograph of hepatic section for Vildagliptin group showed mild centrilobular chronic inflammatory cell infiltration (blue arrow); score 1, H&E, x400; **E** - Photomicrograph of hepatic section for sham group showed moderate periportal chronic inflammatory cell infiltration (blue arrow), with regions of pyknosis and apoptotic bodies in the interface area (yellow arrows); score 2, H&E, x400

Source: Own materials

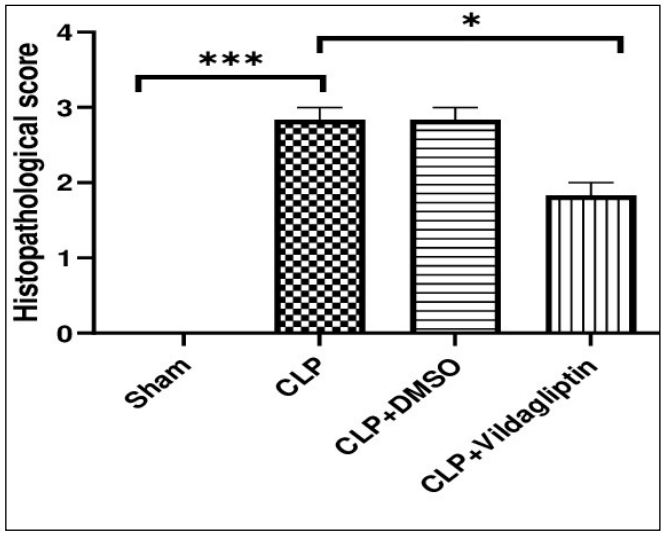

Fig. 8. Impact of vildagliptin on liver injury score. Sham group score 0 Data are presented as mean ±SEM, n=6/group *p<0.05, ***p<0.001
Source: Own materials

current study detected that the serum levels of ALT and AST were elevated in mice subjected to CLP operation in comparison with sham group, coincided with previous report indicating that CLP operation induced liver injury in mice with increased levels of ALT and AST [12, 15]. By contrast, pretreatment with vildagliptin significantly lowered serum concentration of ALT and AST in comparison with CLP group confirming that vildagliptin has protective effect against sepsis induced liver injury. This results are coincided with other study indicating that vildagliptin significantly decreased elevated liver enzyme in rat model with hepatic I /R [16] . Our study represents the first to address vildagliptin protective effect against sepsis induced liver injury. Our results detected marked elevation of IL-6 in liver tissue of CLP group compared to sham group. Several researches are in agreement with our finding [11, 17]. IL-6 is considered a key cytokine up regulated in pathogenesis of sepsis and induced organ injury [18-19]. IL-6 played main role in diagnosis of bacteremia in addition to elevation levels of IL-6 correlated with lowered survival rate in septic patients [20]. Vildagliptin administration showed significant declined of IL-6 in liver tissue. Our result in agreement with previous study documented that vildagliptin treatment significantly lowered IL-6 in rat model with hepatopulmonary syndrome [21]. The present study exhibited marked elevation serum level of MIF in mice exposed to CLP operation compared to sham group. Our finding is in accordance with previous studies [22]. MIF is a main factor played essential role in the development of sepsis and increasing production of IL-6 [23]. To best of our knowledge, no previous research demonstrated the effect of vildagliptin on serum MIF. In addition, current study exhibited significant elevation of hepatic ICAM-1 of CLP group compared to sham group and this result in agreement with previous study [11]. ICAM-1 is regarded as crucial adhesion molecules regulating migration and infiltration of neutrophil during sepsis in addition, Blocked ICAM-1 mitigated sepsis induced organ injury and death [24]. Vildagliptin administration markedly lowered hepatic 1CAM-1compared to CLP group. Furthermore, Wiciński and colleagues confirmed vasculoprotective effects of vildagliptin through reduction expression of ICAM-1 [25]. This study demonstrated a significant elevation of hepatic caspase-11 in CLP group compared to sham group. This results coincided with previous study [15]. LPS induced activation of caspase -11, mediated pyroptosis. However, it considered the main regulator in endotoxemia [26]. Cell pyroptosis played important role in progression of sepsis [27]. In contrast, vildagliptin treatment markedly reduced hepatic caspase-11, no previous researches investigated the effect of vildagliptin administration on caspase-11. To examine the role of autophagy in liver injury induced by CLP operation, LC3 level was determined in hepatic tissue. Current study showed that CLP was associated with significant reduction of hepatic LC3 as compared to sham group. Vildagliptin administration markedly elevated hepatic LC3 compared to CLP group. There is no previous research that documented the effect of vildagliptin on hepatic LC3 during sepsis induced liver injury. Autophagy activation can mitigate sepsis induce organ injury [28], in addition to suppress oxidative stress [29]. In sepsis, the limitation of oxygen supply in addition to damaged antioxidant system resulted in increased ROS and mitochondrial dysfunction [30]. Previous study showed that oxidative stress and inflammation caused tissue damage [31-34]. To investigate the role oxidative damaged MDA, the product of lipid peroxidation was assessed in addition to antioxidant enzymes that played important role in scavenging of free radicles [35-37]. Our results documented significant elevation of MDA alongside with lowered SOD in hepatic tissue of mice which subjected to CLP procedure and this results in agreement with previous study [38]. Vildagliptin administration showed marked declined of hepatic MDA reflecting decreased oxidative stress condition, additionally vildagliptin showed significant elevation of hepatic SOD demonstrating antioxidant effect. Our finding is consistent with study done by Sherif who showed that vildagliptin declined hepatic MDA alongside with elevated antioxidant enzyme activity in rat subjected to hepatic ischemia and reperfusion [10]. The anti-inflammatory and antioxidant of vildagliptin may be related to elevated level of GLP-1 which led to activation GLP-1 receptor [39]. That could have protective effect against mitochondrial

dysfunction [40]. Sharma et al documented that Wnt /B-catenin signaling pathway involved in pathogenesis of sepsis [8]. Our finding revealed that gene expressions of hepatic Wnt and B-catenin markedly elevated in CLP group compared to sham group. Vildagliptin treatment markedly reduced hepatic Wnt/B-catenin. No previous study investigated the effect of vildagliptin on hepatic Wnt/B-catenin during sepsis induced liver injury. Additionally, it was found that sitagliptin inhibit renal Wnt/B-catenin signaling pathway in rat model with diabetic nephropathy [41]. Our study revealed that CLP procedure led to inflammatory cell infiltration, necrosis, pyknosis and cytoplasmic eosinophilia [11]. Vildagliptin administration markedly reduced histopathological changes of hepatic tissues. The Hepatoprotective effect of vildagliptin may be attributed to its anti-inflammatory, antiapoptotic, antifibrotic and antioxidant [42-45].

CONCLUSIONS

Vildagliptin has Hepatoprotective effect during endotoxemia induced liver injury through modulation inflammatory and oxidative stress markers in addition to down regulation of Wnt/B-catenin pathway.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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